

THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN PHANTOM LIMB PAIN

After an amputation many patients awake from the anesthesia feeling certain that the operation has not been performed. They feel the lost limb so vividly that only when they reach out to touch it, or peer under the bed sheets to see it, do they realize it has been cut off. This phenomenon has been termed the *phantom limb* and is usually described as having a tingling or pins-and-needles quality. For purposes of description, classification, and treatment, it is useful to distinguish between the normal, nonpainful phantom limb, and the painful phantom limb. The nonpainful phantom is reported to develop within a day of amputation in approximately a third of patients, and by 8 days the incidence is near 85%.⁴⁴ The percentage of amputees that experience a phantom limb 6 months and 2 years later does not change appreciably, although with time there is a significant decrease both in the frequency with which the phantom limb occurs as well as in the duration of episodes.

For many amputees, however, a distressing problem is phantom limb pain (PLP).⁸⁴ The pain may be an intensification of the tingling sensation that defines the nonpainful phantom limb, or it may consist of paroxysmal shooting pains that travel up and down the limb. The phantom limb may be reported to be in a cramped or unnatural posture that gives rise to excruciating pain. For many amputees, the phantom is the seat of an intense burning pain as if the hand or foot were being held too close to an open flame. In still others, the pain in the phantom limb is indistinguishable from the pain experienced in the

limb prior to amputation. Frequently amputees suffer from several qualities of pain.⁴⁵

The variability in time course of PLP is much greater than that of the non-painful phantom. According to the only prospective study carried out to date, the incidence of PLP 8 days, 6 months, and 2 years after amputation was 72%, 65%, and 59%, respectively, with a reduction over time both in the frequency and duration of attacks.⁴³ The prevalence of PLP is equally grim when the time frame is extended beyond the 2-year mark. More than 70% of amputees continue to experience PLP of considerable intensity as long as 25 years after amputation.⁸⁴ Equally striking is the low success rate of treatments for PLP: in the long term only 7% of patients are helped by the more than 50 types of therapy used to treat PLP.⁸⁴ This intractability reflects our ignorance about the mechanisms that contribute to PLP.

Recently, Sherman⁸⁵ has argued that PLP is not a unitary syndrome, but a symptom class, with each class subserved by different etiologic mechanisms. For example, one class of PLP that is characterized by a cramping quality is associated with EMG spike activity in muscles of the stump, but burning PLP shows no such association.⁸⁵ Katz and Melzack⁴⁹ have identified a class of PLP that resembles in quality and location a pain experienced in the limb before amputation. Although the precise physiologic mechanisms that underlie these somatosensory pain memories are unknown, the presence of preamputation pain is clearly necessary for these phantom pains to develop.

Another class of PLP may come about through involvement of the sympathetic nervous system (SNS). This chapter reviews the theoretical and empirical work that implicates a role for the SNS in contributing to phantom limbs. A brief description of sympathetically maintained pain is followed by a selective review of evidence for a sympathetic-efferent somatic-afferent coupling mechanism based on experimental literature. Involvement of the SNS in an animal model of PLP is then presented and is followed by a review of literature suggesting that the SNS contributes to both nonpainful and painful phantom limbs. A model of phantom limb pain is developed that involves a sympathetic-efferent somatic-afferent cycle of activity, initiated by higher brain centers involved in cognitive and affective processes. Finally, results of treatments that block sympathetic efferent activity are reviewed.

SYMPATHETICALLY MAINTAINED PAIN

The role of the SNS in triggering or maintaining pathologic pain has been a source of considerable confusion and debate.^{11,42,66,70,81} SNS involvement in pain has been attributed to a cycle of sympathetic-efferent somatic-afferent activity in which neural and/or vascular mechanisms participate. Pain is hypothesized to arise from sympathetically triggered ephaptic transmission,⁴⁰ sympathetic activation of nociceptors^{8,22} or low threshold mechanoreceptors that terminate on sensitized spinal cord cells,⁷⁷ and injury-induced alteration in the pattern of postganglionic cutaneous vasoconstrictor neurons, which lose their normal thermoregulatory function leading to trophic changes and ischemia.⁴⁰

Systems for classifying the role of the SNS in pain emphasize different aspects of the disorder. Current thinking distinguishes between sympathetically maintained pain (SMP) and sympathetically independent pain (SIP).⁸ SMP is defined as pain arising from the action of the sympathetic efferents on afferent fibers in injured peripheral tissue; by definition, SMP is abolished when the sympathetic supply to the painful region is blocked.¹¹ In contrast, SIP does not depend on the sympathetic efferents, so that maneuvers directed at blocking peripheral sympathetic activity do

not affect the pain. One of the major advances achieved by this classification is to dissociate the presence of pain from signs of sympathetic dysregulation (e.g., altered temperature, excessive sweating, trophic changes) in the affected region so that evidence of abnormal SNS activity need not accompany SMP.⁹³ A model for SMP has been proposed that involves injury-induced upregulation of alpha-adrenoreceptors on nociceptors and ongoing sensitization of central pain-signaling neurons following adrenergic activation of nociceptors by norepinephrine released from peripheral sympathetic terminals (see Fig. 1 on page 142). Under these conditions, touch evoked pain or allodynia (if present) is hypothesized to develop due to central modulation from ongoing nociceptor activity. Local anesthetic blockade of the sympathetic supply to the involved region temporarily prevents the release of norepinephrine and reverses the state of central sensitization so that both touch-evoked and ongoing pain are relieved.

According to another system of classification,⁴¹ SMP is thought to represent one of three disorders involving the SNS. *Sympathetic algodystrophy* (reflex sympathetic dystrophy) is characterized by ongoing pain, touch-evoked pain, abnormal regulation of blood flow, and sweating and trophic changes. *Sympathetic dystrophy* is distinguished by the absence of spontaneous pain. In this system, the signs of abnormal SNS activity take diagnostic precedence over the response to treatments that block the sympathetic supply to the affected region. Thus, in contrast to the SMP-SIP classification, pain that persists following sympathetic blockade in a patient with clear signs of regional sympathetic dysregulation and ongoing pain would not suggest a diagnosis of SIP, but one of sympathetic algodystrophy, implying that the SNS is somehow involved in maintaining the pain.

Evidence of Sympathetic-Sensory Coupling Following Peripheral Injury

Substantial evidence exists for a sympathetic-efferent somatic-afferent coupling mechanism both in the normal, noninjured state³⁴ and after tissue damage or peripheral nerve injury. However, only in the presence of injury-induced pathophysiology does such sympathetic-sensory coupling contribute to pathologic pain. Jänig⁴¹ has outlined some of the possible modes of coupling between the sympathetic efferents and somatic afferents in injured tissue. These include chemical (e.g., alpha₁-adrenergic) coupling, ephaptic coupling (e.g., direct electrical crosstalk), microenvironmental coupling (e.g., changes in the microclimate of the primary afferent fibers) and indirect coupling in which norepinephrine is postulated to have a presynaptic effect on alpha₂-adrenergic receptors leading to prostaglandin release and a lowering of the primary afferent threshold.⁵⁷ Empirical support for coupling other than that of a chemical nature (i.e., due to release of norepinephrine from postganglionic sympathetic fibers in close proximity to primary afferent fibers) is scant.⁴² In the present context, ephaptic coupling, which is more likely to occur after partial nerve injury (e.g., after high-velocity gunshot injury), is probably an unlikely mechanism for PLP following amputation, but it may be more likely to contribute to PLP following incomplete ruptures or traction injuries of the brachial plexus (as frequently occurs in a motorcycle accident).

Regenerating afferent fibers that are trapped in a neuroma develop a hypersensitivity to intravenous or intraarterial injection of adrenergic agonists and to stimulation of the sympathetic supply of the neuroma (Fig. 1).^{6,25,52,79,96} In addition, chemical coupling is abolished following administration of the alpha-adrenergic receptor antagonist phentolamine but usually not after beta-adrenergic blockade.^{6,25,52,96} These

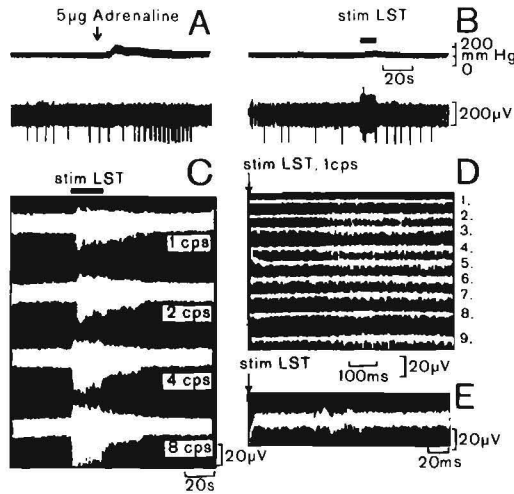


FIGURE 1. Responses of myelinated (A, B) and unmyelinated (C-E) afferent fibers in cat (A, B) and chronic rat (C-E) neuromas to intravenous injection of 5 µg of adrenaline and electrical stimulation of the lumbar sympathetic trunk (LST). C, stimulation of the LST at frequencies that mimic the physiologic discharge rate of sympathetic efferents (i.e., 1–4 Hz) produced activation of unmyelinated afferents in a neuroma of a rat's sciatic nerve 8.5 months after sciatic and saphenous nerve transections. D, evidence of "wind-up" (increased responsiveness) following repetitive LST stimulation at 1 Hz. E, activity in postganglionic axons in a branch of the posterior biceps nerve by electrical stimulation of the central cut end of the nerve. (From Blumberg H, Jänig W: Neurophysiological analysis of efferent sympathetic and afferent fibers in skin nerves with experimentally produced neuromata. In Siegfried J, Zimmermann M (eds): Phantom and Stump Pain. New York, Springer-Verlag, 1981, pp 15–31; with permission.)

findings form the basis of the hypothesis that paresthesias, dyesthesias, and pain may arise from sympathetic-sensory chemical coupling in damaged tissue.⁷⁷

Devor and colleagues^{25,52} have shown that sympathetic-sensory coupling not only occurs in the periphery within experimental neuromas but that activity in dorsal root ganglion (DRG) cells can also be modulated by sympathetic activation after transection of the sciatic nerve.²⁶ Responses both to electrical stimulation of preganglionic sympathetic efferents and systemically administered adrenaline were blocked by phentolamine. The various modes of sympathetic-sensory coupling⁴¹ may also develop in DRG. The recent finding that injury to the sciatic nerve is followed by sprouting of sympathetic efferents around large-diameter cell bodies in the DRG⁶¹ increases the potential for sympathetic-sensory coupling and makes the DRG a likely and heretofore unsuspected source of sympathetically triggered pain and dyesthesias.²⁶

THE AUTOTOMY MODEL OF PHANTOM LIMB PAIN

Wall et al.^{95,97} developed a rodent model of *anesthesia dolorosa* in which peripheral neurectomy is followed by self-mutilation behavior termed *autotomy*. In the autotomy model, the sciatic and saphenous nerves of the rat are transected at midthigh level, resulting in complete anesthesia and loss of motor function in the peripheral territories subserved by these nerves. Within 1–3 weeks of denervation, the rats begin to bite and scratch the distal portions of the insensitive paw to the

point of amputation. Although there is a controversy over the interpretation of the self-mutilative behavior,^{56,78} most researchers do not doubt that autotomy is a response to pain or dysesthesias referred to the anesthetic limb and therefore represents an animal model of PLP.^{16,24} Since the hindpaw is still present, the autotomy model more closely resembles conditions in humans that arise after complete brachial plexus ruptures or dorsal root avulsions. Nevertheless, because the nerve sections produce a deafferentation of the entire hindpaw, it is inferred that any pain or dysesthesias experienced in the denervated territory must be phantom pain. The nature of the autotomy behavior in rats parallels reports of PLP in human amputees. It is not uncommon for amputees to report brief bouts of paroxysmal pain that is experienced as arising from the phantom limb. Observation of rats with denervated hindpaws reveals similar bouts of self-mutilative behavior, presumably due to pain and/or dysesthesias referred to the denervated paw.

Evidence of Sympathetic-Sensory Coupling in the Autotomy Model

Not only do procedures that enhance or mimic sympathetic outflow increase autotomy levels, but those that reduce or block sympathetic activity decrease the degree of autotomy. Thus, autotomy is enhanced by the monoamine oxidase inhibitor pargyline,¹⁰⁰ which increases norepinephrine storage and release from peripheral sympathetic terminals. Administration of the antisympathetic agent guanethidine, which in adult rodents acts by preventing the release of norepinephrine from sympathetic nerve terminals, has been shown to reduce autotomy.^{14,18,97} Likewise, the incidence of autotomy is significantly reduced among rats treated with guanethidine for 10 days beginning 2 days after birth.²⁰ Moreover, neonatal guanethidine sympathectomy not only reduced the self-mutilative behavior relative to controls but also suppressed the changes in spinal norepinephrine normally observed among untreated animals 15 and 60 days after sciatic and saphenous nerve sections.

Although it has been argued^{6,42} that excitation of afferents within an acute experimental neuroma by relatively high-frequency electrical stimulation (10–25 Hz) of the lumbar sympathetic trunk (LST) may not have clinical relevance due to the nonphysiologic rates required to elicit afferent activity, Jänig³⁹ reported that low-frequency electrical stimulation (1–8 Hz) of the sympathetic supply, but not intravenous adrenaline, elicits activity in C-fibers 8.5 months after sciatic and saphenous nerve transections (Fig. 1C). Afferent fibers, which were activated by rates of LST within the physiologic range of sympathetic efferent fibers (i.e., 1–4 Hz), displayed characteristics suggestive of wind-up (Fig. 1D); repeated LST stimulation resulted in increasingly greater responsiveness (although by 1–2 hours after the onset of stimulation, all units had stopped responding). The failure of adrenaline to elicit afferent activity within the neuroma raises the question of the nature of the postganglionic sympathetic-efferent somatic-afferent coupling mechanism. Nevertheless, that low-frequency electrical stimulation of the LST was capable of evoking afferent activity provides indirect evidence for the possibility that physiologic levels of sympathetic activity may contribute to autotomy behavior in certain animals. Furthermore, the finding that such stimulation was effective in a chronic neuroma, 8.5 months after denervation, provides a mechanism whereby normal levels of sympathetic activity might evoke chronic PLP and dysesthesias long after amputation.

Effects of Sympathetic Activity on Autotomy Levels

A growing body of clinical and laboratory data shows that injury produces prolonged changes in central nervous system function, which influence responses to

subsequent somatosensory inputs. The data strongly suggest that this injury-induced neuroplasticity may contribute to the experience of pain long after the offending stimulus has been removed or the injury has healed.¹⁷

The most striking clinical evidence of injury-induced central neuroplasticity in humans comes from studies of amputees who report PLP that resembles a pain experienced in the limb before amputation.⁴⁹ For example, amputees may report the sensation of a painful preamputation ulcer on the phantom foot or the burning pain of gangrene that was present at the time of amputation. These somatosensory pain "memories" are not merely cognitive recollections but are direct experiences of pain that are referred to the phantom limb in the same location and with the same qualities of sensation as the past pain.

The autotomy model described above also has been used to explore the effects of a prior injury on the subsequent development of pain referred to the anesthetic limb in an attempt to model the observations among human amputees that preamputation pain persists as PLP following amputation. Studies have shown that chemical or thermal injury of the paw prior to deafferentation increases the severity of autotomy or leads to a shift in the site of self-mutilation.^{19,50} Since all sensory input from the injured paw is eliminated as a consequence of deafferentation, the enhanced autotomy has been attributed to increased pain due to the sensitization of central cells by the earlier injury, thus reflecting a change in central neural function that long outlasts the duration of injury.

Coderre^{15,18} examined the effects of altering sympathetic activity or central monoaminergic activity on autotomy levels among animals with or without hindpaw injuries induced prior to sciatic and saphenous nerve sections. In one study,¹⁵ rats received bilateral electrolytic lesions or sham lesions of central noradrenergic neurons in the locus coeruleus, which are known to exert a tonic inhibitory influence over dorsal horn neurons. Autotomy progressed more rapidly among lesioned rats that received an injury prior to denervation although the degree of autotomy did not differ from lesioned animals that did not receive a prior injury. In a second study,¹⁸ the enhancement of autotomy that typically develops when a paw is injured prior to denervation was decreased by a combination of intrathecal capsaicin and guanethidine, but not by guanethidine (or capsaicin) alone, suggesting that both C-fiber activity and sympathetic outflow are critical to the heightened autotomy. In contrast, intrathecal guanethidine alone, but not the combination of capsaicin and guanethidine, was effective in reducing autotomy among uninjured rats. One implication of these findings is that, in the presence of CNS sensitization (e.g., due to a prior injury), procedures designed to treat PLP by reducing the afferent or efferent limb of a sympathetic-sensory cycle of activity may not be effective until both C-fiber activity and sympathetic efferent activity are abolished.

Heritability of Neuropathic Pain

One of the more exciting lines of recent research raises the issue of the heritability of neuropathic pain conditions in humans. Using the autotomy model, Devor and Raber²⁷ developed two lines of rats by interbreeding those that exhibited high levels of autotomy and those that showed low levels of autotomy. Offspring had their sciatic and saphenous nerves transected, and rats that showed high levels of autotomy were interbred, as were those that showed low levels of autotomy. Interbreeding by selecting for high- or low-autotomy behavior was carried out for 13–15 generations. From the third generation onward, high- and low-autotomy rats could be distinguished by level of self-mutilation. In addition, there was a signifi-

cant decrease over the generations in the variability of autotomy within lines so that by the 11th generation the incidence of autotomy approached 90% among the high-autotomy line and was approximately 10% among the low-autotomy line. Moreover, the kinetics of the self-mutilative behavior were altered as a function of generation with a shift to a much earlier onset after denervation among high-autotomy animals as the interbreeding continued. Rather than beginning approximately 3 weeks after nerve section, successive generations showed autotomy onset as early as the first week. Twelfth generation high autotomy rats showed significantly greater sensitivity on sensory and thermal testing than low-autotomy rats. Based on the pattern of autotomy among hybrid rats and backcrossed hybrids, the authors suggested that the mode of inheritance of the autotomy trait is through a single autosomal recessive gene. Whether the two lines of rats differ in their relative sensitivity to sympathetically generated afferent activity or background level of sympathetic outflow has not yet been established (Devor, personal communication), but autotomy levels have been found to differ as a joint function of the strain of rat and the level of environmental stress,⁹⁹ suggesting that genetic differences in sympathetic outflow may account for the pain-related behavior under stressful conditions. The strong genetic component associated with the autotomy trait raises the possibility that some patients may inherit a predisposition to develop chronic neuropathic pain after amputation.²⁷

PHANTOM LIMB PAIN

The detailed and highly technical work carried out with experimental neuromas stands in stark contrast to the dearth of information on the role of the SNS in PLP among human amputees. Generally, reports are poorly controlled or uncontrolled and are based on small sample sizes, making generalization questionable. Furthermore, with the exception of more recent studies, PLP (and pain relief, if a treatment is involved) is not assessed with sufficient attention to important parameters such as quality, frequency, intensity, and duration. This criticism is especially relevant in the light of the multiple mechanisms and levels of the PNS and CNS that have been proposed to contribute to PLP. For example, the findings⁸⁵ that cramping phantom limb pain correlates with EMG measurements but not blood flow at the stump and that burning stump and phantom limb pain correlate with stump blood flow but not EMG recordings underscores the importance of assessing the quality of the pain reported by patients with PLP.

Involvement of the Sympathetic Nervous System

Evidence of sympathetic involvement among amputees with PLP comes from studies that pharmacologically block^{58,59} or surgically interrupt^{4,46} the sympathetic supply to the involved limb, producing at least temporary alleviation of pain. Long-term relief of PLP has been reported with propranolol, a beta-adrenergic blocking agent, but these reports are uncontrolled and unblinded.^{1,60,72} An open trial of propranolol in 6 (nonamputee) patients with pain from peripheral nerve injuries showed little benefit.⁸⁰ Electrical or mechanical stimulation of the lumbar sympathetic chain produces intense pain referred to the phantom limb,^{31,67} whereas sensations are referred to the abdomen or flank in pain patients without amputation.⁶⁷

Regional sympathetic hyperactivity also has been hypothesized to contribute to the development of PLP through excessive vasoconstriction and sweating at the stump and surrounding regions.⁵⁹ The condition may spread centrally from the stump to involve the phantom limb. Hyperalgesia (heightened pain) and allodynia (pain arising from gentle touch) may be referred to the phantom limb upon stimula-

tion of the stump regardless of whether the stump is painful or shows signs of trophic or vascular changes.^{30,58} The characteristic qualities of superficial burning pain and deep aching pain may provide additional evidence of SNS involvement.³⁰ However, just as some sympathetically maintained pains occur in the absence of regional sympathetic abnormalities,⁸ not all patients with phantom limb pain due to SNS involvement would be expected to show signs of abnormal SNS activity at the stump (e.g., trophic changes, abnormal sympathetic reflexes and sweating, alterations in stump blood flow). This possibility suggests that the abnormality associated with sympathetically maintained pains of this type does not reside in the SNS but in the afferent supply of the involved extremity.^{81,93} The absence of signs of SNS abnormality points to the importance of diagnostic sympathetic blocks, the phentolamine test, or regional infusions of guanethidine to ascertain the presence of SMP.

Even when SNS abnormalities are present, their relationship to pain in the stump and pain in the phantom is not always clear-cut.⁹² For example, Livingston⁵⁸ reports cases of amputees with phantom limb pain who also showed abnormalities in sweating and large temperature differences between the stump and contralateral intact limb but who did not complain of stump pain. Local anesthetic infiltration into the sympathetic ganglia was followed by relief of phantom limb pain, a sense of warmth and relaxation in the phantom, and a reversal of the vasomotor, sudomotor, and trophic changes at the stump, all of which often extended well beyond the duration of action of the local anesthetic. Despite the correlation between the restoration of normal sympathetic functioning and the relief of phantom limb pain, it remains unclear whether the sympathetic abnormalities were responsible for the pain or whether both were caused by a common third factor (e.g., reduced sympathetic transmitter release).

Nyström and Hagbarth⁶⁹ carried out microneurographic recordings of activity from skin and muscle nerve fascicles in two amputees with PLP. One patient had sustained a below-knee amputation and suffered from intense cramping pain referred to the phantom foot. Recordings from muscle nerve fascicles in the peroneal nerve showed that although bursts of activity in sympathetic fibers were accentuated by the Valsalva maneuver, the phantom pain remained unchanged, suggesting that the pain was not dependent on sympathetic activity. The second patient had undergone amputation of his left hand at the wrist secondary to extensive lacerations following an agricultural accident. Microneurographic recordings were taken from a skin nerve fascicle in the left median nerve at the wrist. In both patients, tapping the neuroma at the stump evoked marked neural activity, afterdischarge, and an intensification of the PLP. Interestingly, although local anesthetic infiltration into the tissue of the stump surrounding the neuroma abolished (or reduced) the tap-induced increase in neural activity and PLP, in neither patient was the spontaneous or background neural activity and PLP changed. In the light of Devor's^{26,28} recent work, the ongoing neural activity that persisted after lidocaine infiltration may well have originated in the DRG and propagated antidromically to reach the recording electrode in the stump.²³

Further evidence of a possible connection between the SNS and pain after amputation comes from a single-blind study¹³ of nine amputees with stump pain, three of whom had concomitant PLP. They received successive perineuromal injections of normal saline (0.5 ml), epinephrine (5 µg in 0.5 ml normal saline) and lidocaine (1 ml 1%). Within 1–2 seconds of injection of epinephrine all patients reported an increase in the intensity of local stump pain, but only one of the three patients with PLP noted an increase in PLP (Fig. 2).

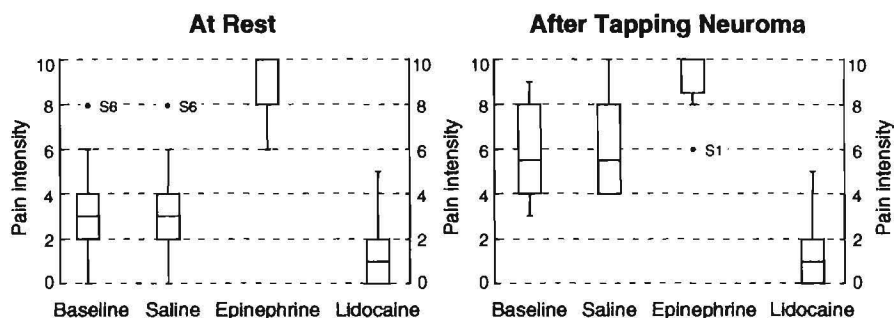


FIGURE 2. Pain intensity reported by amputees before (baseline) and after perineuromal injection of saline, epinephrine, and lidocaine, shown for conditions of rest and after tapping the neuroma. Median values correspond to the horizontal line partitioning each box; the first and third quartiles are represented by the ends of the boxes. Individually identified patients (e.g., S1, S6) represent relatively unusual values. Note the significant increase in pain following injection of epinephrine and the reduction following lidocaine injection. (Data from Chabal C, Jacobson L, Russell LC, Burchiel KJ: Pain response to perineuromal injection of normal saline, epinephrine, and lidocaine in humans. *Pain* 49:9–12, 1992.)

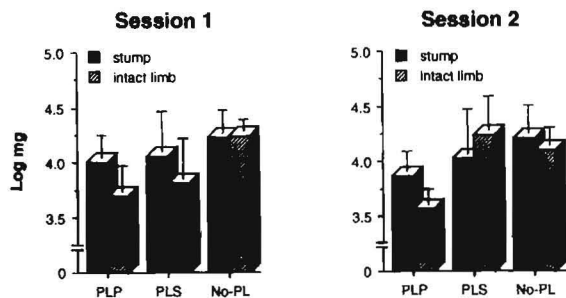
The quality of the pain following injection of epinephrine was described as “poorly localized shooting or electric shock-like” while the area of discomfort increased from baseline. Four patients remarked that the limb was “on fire.” Lidocaine injection significantly decreased but did not abolish the pain. Five patients who received a control injection of subcutaneous epinephrine (5 μ g in 0.5 ml normal saline) in a region distant from the neuroma reported a localized, minor stinging lasting 1–2 seconds and described it as distinctly different from the pain experienced in response to perineuromal injection of epinephrine. Unlike the results of Wallin et al.⁹⁸ in which hyperalgesia developed in a previously sympathectomized (nonamputee) patient 30 minutes after iontophoretic application of epinephrine, the immediate response of these patients to perineuromal injection of epinephrine suggests a direct alpha-adrenergic coupling mechanism; however, the possibility of indirect chemical or microenvironmental coupling cannot be excluded.

The Relationship Between Phantom Limbs and Correlates of SNS Activity at the Amputation Stump

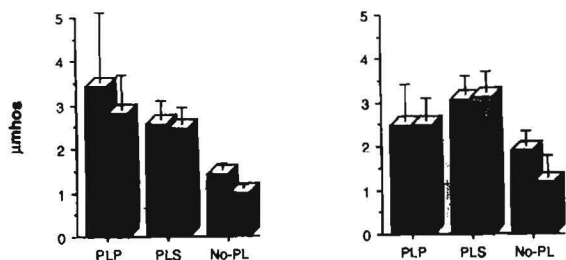
Despite the frequent assertions that the SNS is involved in the production and maintenance of PLP, surprisingly few studies have actually examined peripheral SNS activity at the stump and contralateral limb. Sliosberg⁸⁹ studied 141 amputees and found that the stump was cooler than the intact limb in 94 patients, but he did not relate the temperature difference to the presence or absence of PLP. Kristen et al.⁵⁴ reported that a “patchy asymmetrical temperature” distribution of stump thermograms was significantly more frequent among stump pain sufferers than in patients who were free from stump pain, but thermograms were no different for patients with or without PLP.

In contrast, Sherman and colleagues^{83,86} observed a negative correlation between temperature at the stump and the presence of burning, tingling, or throbbing phantom limb and stump pain, indicating that reduced blood flow to the stump is associated with increased levels of pain. Repeated measurements of the same patients on different occasions revealed that lower temperatures at the stump relative to the

Pressure Sensitivity Threshold



Skin Conductance



Skin Temperature

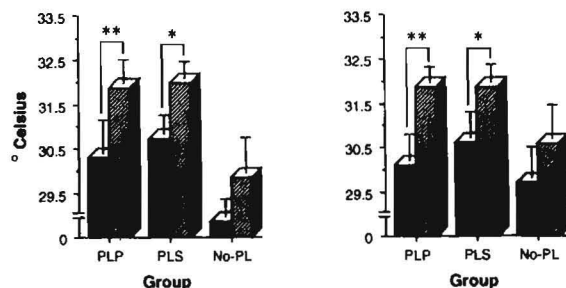


FIGURE 3. Mean pressure sensitivity thresholds, skin conductance, and skin temperature of the stump and contralateral limb displayed for three groups of amputees on two sessions separated by at least 24 hours. PLP = phantom limb pain; PLS = nonpainful phantom limb sensations; No PL = no phantom limb at all. Mean stump skin temperature was significantly lower than the contralateral limb for Groups PLP (** $p < .005$) and PLS (* $p < .05$) but not Group No PL. (From Katz J: Psychophysical correlates of phantom limb experience. *J Neurol Neurosurg Psychiatry* 55:811–821, 1992; with permission.)

contralateral limb were associated with greater intensities of phantom limb and stump pain, suggesting that the reduced blood flow was somehow causally tied to the pain. However, because the relationship between phantom pain and limb temperature was confounded by coexisting stump pain in most cases, it is not possible to unambiguously attribute the presence of PLP to altered blood flow at the stump. Since stump pain was a significant problem for most patients (regardless of whether they also had PLP), it is not surprising that blood flow was reduced at the stump relative to the intact limb.⁵⁴ The presence of abnormal blood flow and sweating are common features of certain sympathetically maintained pains,⁴¹ and there is no reason to assume that patients with burning stump pain might not also show decreased stump temperature. In order to claim that phantom limb pain is associated with sympathetic dysregulation at the stump, it is necessary to compare the two limbs in patients suffering from PLP but not stump pain. In addition, the absence of

a control group of amputees without PLP (i.e., with painless phantom limb sensations or no phantom limb at all), raises the possibility that decreased stump blood flow is a characteristic of all stumps regardless of the patient's status with respect to PLP. Pain does not always accompany temperature differences between the involved and noninvolved limb in patients with peripheral nerve injuries.⁶⁶

Following this line of inquiry, Katz⁴⁷ compared skin conductance and surface skin temperature of the stump and contralateral limb in amputees reporting PLP (Group PLP), nonpainful phantom limb sensations (Group PLS), or no phantom limb at all (Group No PL). The results showed that although mean skin temperature was lower at the stump than the contralateral limb in all groups, the difference was significant for Groups PLP and PLS but not Group No PL (Fig. 3). Stump-intact limb temperature differences in excess of -1°C were associated with the presence of a phantom limb in the absence of concomitant stump pain (Table 1).

These results suggest that the presence of a phantom limb, whether painful or painless, is related to the sympathetic-efferent outflow of cutaneous vasoconstrictor fibers in the stump and stump neuromas. The related finding that stump skin conductance responses over time correlated significantly with the intensity of phantom limb paresthesias, but not other qualities of sensation, supports the hypothesis (outlined below) of a sympathetic-efferent somatic-afferent mechanism involving both sudomotor and vasoconstrictor fibers. The most parsimonious explanation of these findings is that the paresthetic or dysesthetic component of the phantom limb may be triggered by sympathetic-efferent activity.

Psychophysical Correlates of Phantom Limb Paresthesias

Although a normal phantom occurs whenever nerve impulses from the periphery are blocked or otherwise removed,⁹⁴ it is also true that direct stimulation of the

TABLE 1. Mean Stump-Intact Limb Difference Scores for Pressure Sensitivity Thresholds, Skin Conductance, and Skin Temperature

	Session 1		
	Group PLP (n = 11)	Group PLS (n = 9)	Group No PL (n = 8)
Pressure sensitivity thresholds (log mg)	0.31 (1.3)	0.25 (1.2)	-0.004 (0.5)
Skin conductance (μmhos)	0.61 (3.0)	0.11 (0.7)	0.43 (0.4)
Skin temperature (°Celsius)	-1.59* (1.8)	-1.26* (1.3)	-0.88 (1.9)
	Session 2		
	Group PLP (n = 11)	Group PLS (n = 9)	Group No PL (n = 8)
Pressure sensitivity thresholds (log mg)	0.30 (0.6)	-0.21 (0.6)	0.11 (0.7)
Skin conductance (μmhos)	0.02 (1.7)	-0.06 (1.5)	0.74 (0.9)
Skin temperature (°Celsius)	-1.75 (1.8)*	-1.25 (1.5)*	-0.85 (2.0)

* Significantly different ($p < 0.05$) from Group No PL.

Information is presented for three groups of amputees on two sessions separated by at least 24 hours. Standard deviations are shown in parentheses. Stump-intact limb difference scores were obtained by subtracting measurements taken at the intact limb from those at the stump. Negative difference scores indicate that relative to the intact limb the stump is lower in skin temperature, lower in skin conductance, and more sensitive to applied pressure. PLP = phantom limb pain; PLS = nonpainful phantom limb sensations; no PL = no phantom limb. (From Katz J: Psychophysical correlates of phantom limb experience. *J Neurol Neurosurg Psychiatry* 55:811-821, 1992; with permission.)

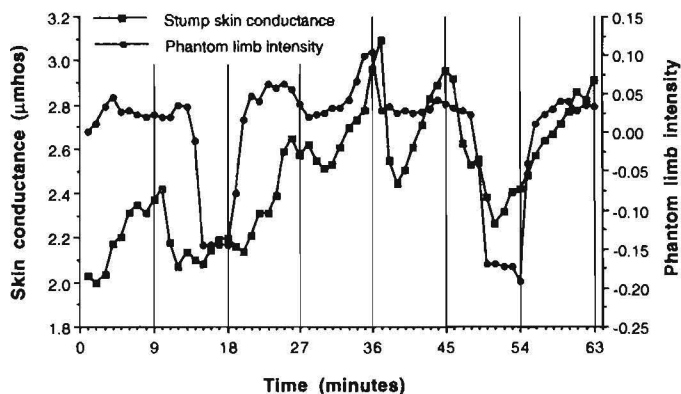
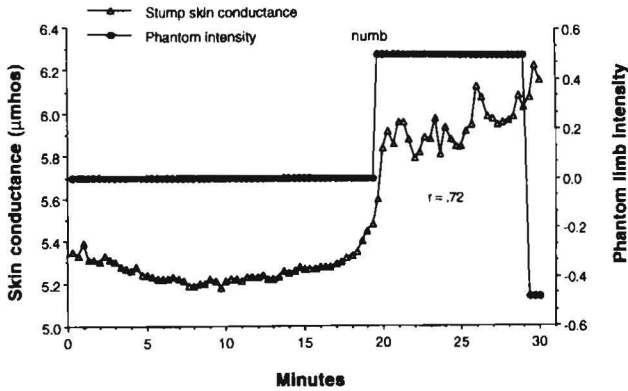


FIGURE 4. A minute-by-minute plot of the relationship between stump skin conductance and the intensity of nonpainful phantom limb paresthesias for a patient with an amputation above the knee and paresthesias referred to the phantom foot and toes. Skin conductance was continuously measured at the stump over a 63-minute period while the patient monitored the intensity of the phantom limb by turning a dial. Phantom limb intensity ratings have been transformed so that a value of 0.0 represents the intensity at the start of the session and deviations from zero correspond to increases and decreases in phantom limb intensity. Each data point represents a mean of 30 values consecutively sampled at 2-second intervals. Changes in the intensity of paresthesias (described by the patient as increases and decreases in “numb” sensations referred to the phantom toes) occur in concert with changes in stump skin conductance. (From Katz J, France C, Melzack R: An association between phantom limb sensations and stump skin conductance during transcutaneous electrical nerve stimulation (TENS) applied to the contralateral leg: A case study. *Pain* 36:367–377, 1989; with permission.)

amputation stump frequently exaggerates the tingling or paresthetic quality of sensation typical of the painless phantom limb.¹² Careful questioning of amputees reveals that the nonpainful phantom limb is not perceived as a static phenomenon. The paresthetic quality of sensation, which defines the phantom limb percept, is in a constant state of flux, with changes occurring in intensity, body part, or both. For example, Katz et al.⁴⁸ reported on a patient whose phantom sensations consisted of a numbness that defined a region including the lateral three toes. Within this circumscribed area, he experienced rapid “waves of numbness” that increased and decreased the intensity of the involved phantom parts.

One mechanism that has been proposed to account for the paresthetic component of the phantom limb is a cycle of sympathetic-efferent somatic-afferent activity.^{47,48} As shown in Figures 3–5, stump skin conductance levels correlate significantly over time with the intensity of phantom limb paresthesias. It is hypothesized that changes in the intensity of phantom limb paresthesias reflect the joint activity of cholinergic (sudomotor) and noradrenergic (vasomotor) postganglionic sympathetic fibers on primary afferents located in the stump and stump neuromas. Release of acetylcholine and norepinephrine from postganglionic sympathetic fibers produces transient vasoconstriction and heightened skin conductance responses. Also, neurotransmitter release onto apposing peripheral fibers trapped in stump neuromas increases primary afferent discharge. This information is transmitted rostrally, where it gives rise to referred phantom sensations upon reaching central structures subserving the amputated parts of the limb. The moment-to-moment fluctuations in the intensity of phantom limb paresthesias reported by many amputees may, in part,

Case E02



Case E08

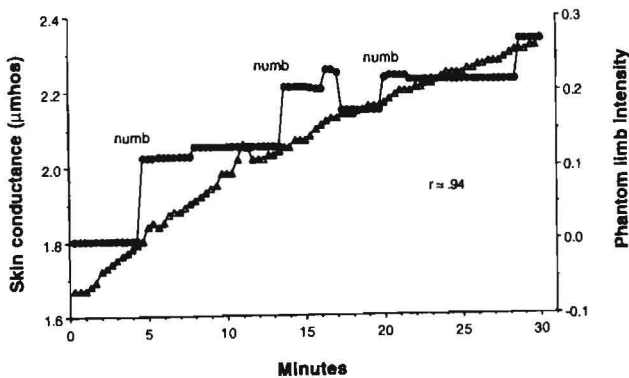


FIGURE 5. Plots of the relationship between stump skin conductance and the intensity of phantom limb paresthesias for two patients with nonpainful phantom limb paresthesias. Skin conductance was measured at the stump over a 30-minute period while the patients monitored the intensity of the phantom limb by turning a dial. Each data point represents a mean of three values consecutively sampled at 10-second intervals. Changes in the intensity of paresthesias (described as increases and decreases in “numb” sensations referred to the phantom limb) occur in concert with changes in stump skin conductance. Also shown is the correlation coefficient describing the strength of the relationship between the two variables and the patient’s descriptions of the quality of the phantom sensation. (From Katz J: Psychophysical correlates of phantom limb experience. *J Neurol Neurosurg Psychiatry* 55:811–821, 1992; with permission.)

reflect a cycle of sympathetic-efferent somatic-afferent activity. Increases in the intensity of phantom limb paresthesias would follow bursts of sympathetic activity, and decreases would correspond to periods of relative sympathetic inactivity.^{47,48} If central sensitization has also developed either through prior injury, trauma during amputation, or peripheral inflammation, or if the sympathetic-sensory coupling involves nociceptors,⁷⁷ the sensation may be one of dysesthesia.

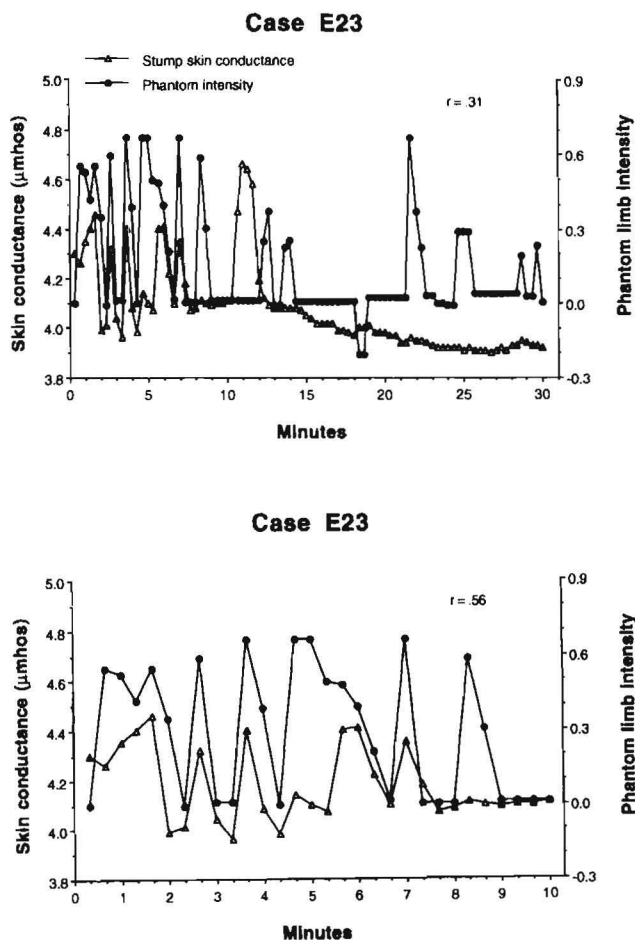


FIGURE 6. The relationship between stump skin conductance and phantom limb intensity for another amputee with phantom limb paresthesias shown for a 30-minute session (Top). The bottom panel shows only the first 10 minutes of the same session, when the two measures showed a prominent tendency to covary. All changes in phantom limb intensity were described by the subject as increases and decreases in “numbness” experienced in the phantom foot. (From Katz J: Psychophysical correlates of phantom limb experience. *J Neurol Neurosurg Psychiatry* 55:811–821, 1992; with permission.)

The possibility that heightened electrodermal activity at the stump occurs as a consequence of the perception of a change in the intensity of paresthesias does not appear to be tenable, since shooting pains, somatosensory memories, and phantom limb movements do not also correlate with stump skin conductance (Fig. 7).⁴⁷ That is, changes in stump skin conductance are related only to the perception of paresthesias (Figs. 4–6) and not to other qualities of sensation (Table 2).

The precise role of postganglionic sudomotor fibers in generating phantom limb paresthesias is not known. The possibility exists that the relationship between stump skin conductance levels and phantom limb paresthesias reflects a direct

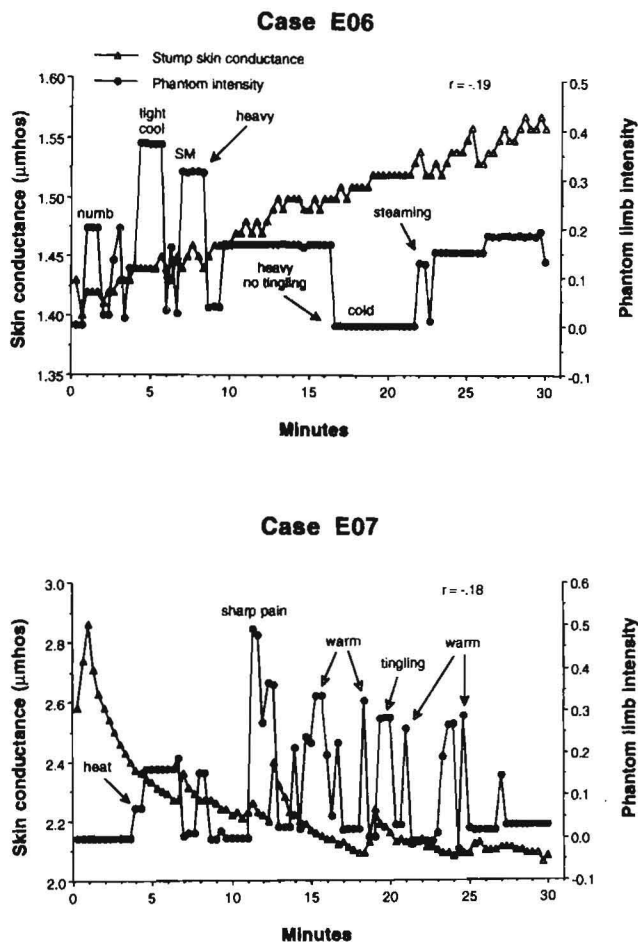


FIGURE 7. Plots of the relationship between stump skin conductance and various qualities of phantom limb pain for two patients in Group PLP. Unlike Figs. 4–6, there is no relationship between stump skin conductance and the intensity of phantom limb pain. (From Katz J: Psychophysical correlates of phantom limb experience. *J Neurol Neurosurg Psychiatry* 55:811–821, 1992; with permission.)

cholinergic-afferent coupling mechanism²⁹ but peripheral sudomotor blockade with atropine in patients with sympathetically maintained pain failed to have an immediate analgesic effect, suggesting that the cholinergic limb of the SNS does not contribute to SMP.³² Another possibility is that since stump skin conductance provides a more accurate indication of postganglionic discharge than surface skin temperature and sudomotor and vasomotor fibers tend to discharge in tandem,⁵ skin conductance responses may merely be a marker for an adrenergic-afferent coupling mechanism generated by epinephrine release following activity in post-ganglionic vasomotor fibers.

Several lines of indirect evidence support the hypothesis that moment-to-moment fluctuations in the intensity of phantom limb paresthesias reflects sympa-

TABLE 2. Relationship Between Phantom Limb Intensity and Stump Skin Conductance and Stump Skin Temperature

	Group PLP (n = 11)	Group PLS (n = 9)	p value
Correlation coefficient (r):			
Phantom limb intensity and stump skin conductance	-0.02	0.29**	0.01
Phantom limb intensity and stump skin temperature	0.06	-0.17	ns*
Number of significant rs:			
Phantom limb intensity and stump skin conductance	6/19 (32%)	8/12 (67%)	0.06
Phantom limb intensity and stump skin temperature	8/19 (42%)	5/12 (42%)	ns*

* Not significant ($p > 0.05$)

** Significantly ($p < 0.05$) different from zero.

Mean Pearson correlation coefficients (r) for patients with phantom limb pain (Group PLP) and non-painful phantom limb paresthesias (Group PLS) describing the linear relationship between phantom limb intensity and stump skin conductance and phantom limb intensity and stump skin temperature. Also shown for each group is the number of significant ($p < 0.002$) correlations between phantom limb intensity and stump skin conductance and between phantom limb intensity and stump skin temperature. P values correspond to the Chi-square test and ANOVA F-test for between-group comparisons of frequencies and means, respectively.

thetic-afferent coupling. First, sympathetic activity in the form of skin conductance responses and changes in skin temperature reflect the activity of postganglionic sudomotor and vasomotor fibers, respectively.^{5,33} Multiunit sympathetic activity recorded from skin nerve fascicles in awake humans shows a strong relationship to effector organ responses including vasoconstriction and sweat gland activity.^{5,33} These studies demonstrate that bursts of activity in sudomotor and vasomotor fibers are reliably followed by transient electrodermal responses and plethysmographic signs of vasoconstriction within the region of skin subserved by the sympathetic fibers under study.

Second, intraneural recordings from sensory nerve fascicles in conscious humans reveals a remarkably strong relationship between the perception of non-painful paresthesias and spontaneous bursting activity in afferent fibers.^{68,71} Finally, non-noxious percutaneous electrical stimulation of afferent nerves located in the stump of forearm amputees produces paresthesias referred to a localized region of the phantom hand but not the stump. Subsequent alterations in the amplitude of electrical stimulation are paralleled by corresponding perceptual changes in the intensity of phantom limb paresthesias.²

Taken together, these studies suggest that the paresthetic component of the phantom limb may in part represent the perceptual correlate of a central autonomic mechanism that operates on peripheral structures. This mechanism is described further in the following section to explain how psychological and emotional processes might alter phantom limb sensations through their actions on the SNS. Direct support for this hypothesis is not available and would require that changes in the intensity of phantom limb paresthesias (or dysesthesias) be correlated with microneurographic recordings from postganglionic sympathetic and primary afferent fibers in amputation stump neuromas.

Psychological and Emotional Processes Influence Phantom Limb Experience

The idea that emotional and psychological processes can cause pain traditionally has been tied to the notion of psychopathology. However, it is becoming in-

creasingly clear that under certain circumstances pain may be triggered by these processes in psychologically healthy individuals as well. It is commonly accepted that anxiety or stress influences pain perception and subsequent behavior.⁶⁴ The aggravation or alleviation of pain referred to phantom body parts also may be mediated in part by psychological processes that alter anxiety levels.⁵¹ Phantom breast pain after mastectomy is provoked by emotional distress in 6% of women 3 weeks after surgery and in 29% a year later.⁵⁵ Fifty percent of lower extremity amputees report that attacks of PLP are triggered by emotional distress⁴³ as long as 7 years after amputation.⁵³ A combination of progressive relaxation training and EMG biofeedback of stump and forehead muscles produces significant reductions of PLP and anxiety⁸² that are sustained for up to 3 years.⁸⁷ Finally, stress levels and pain intensity ratings sampled over a 180-day observation period correlate significantly for most amputees.³

There are also examples of psychological or emotional processes precipitating transient but profound alterations in the quality and intensity of phantom limb sensations. These processes include concentration,⁶⁵ distraction,⁷³ relaxation,^{82,87} fright,³⁵ forceful reminders of the events that led to amputation,⁸⁸ and witnessing cruel and violent acts.^{74,91} One amputee interviewed by this writer described his reaction to an accident involving his wife by reporting “. . . goose bumps and cold shivering down the phantom [leg]. It went through me. Everything emotional will get you that.” Another amputee stated, “It’s like everything I feel goes there—the good and the bad.”

A Centrally Triggered Sympathetic-Efferent Somatic-Afferent Mechanism

The material presented above indicates that cognitive and affective processes reliably trigger transient pains or sensations referred to the phantom limb. The model schematically represented in Figure 8 outlines a mechanism through which cognitive and affective processes associated with higher cortical and limbic centers may alter phantom limb sensations. The reciprocal connections between cortical, limbic, and lateral hypothalamic structures are well documented.^{7,90} The lateral hypothalamus is involved in the control and integration of neural activity associated with affectively-charged behavior^{7,62,90} and has direct projections to the lateral horn of the spinal cord. The intensity of phantom limb paresthesias and dysesthesias may thus be modulated by higher brain centers involved in cognitive and affective processes via a multisynaptic network of descending inputs that impinges on pre-ganglionic sympathetic neurons producing diffuse peripheral autonomic discharge and activation of primary afferent fibers located in stump neuromas.

Occasionally, the effects of intense affect (e.g., fright, horror) are experienced diffusely over the entire body as cutis anserina associated with pilomotor contraction (i.e., goose bumps). Among amputees, however, a more frequent occurrence is that the perception of less salient events and emotions precipitates these sensations throughout only the phantom limb. The tendency for affectively charged and psychologically meaningful experiences to be referred to the phantom limb, but not to other parts of the body, is consistent with two lines of evidence suggesting that the threshold for impulse generation is lower both in regenerating primary afferents in the stump and in deafferented central cells subserving the phantom limb than in the intact nervous system.

First, regenerating sprouts, which are trapped in a neuroma, are exceedingly sensitive to the postganglionic sympathetic neurotransmitters norepinephrine⁹⁶ and

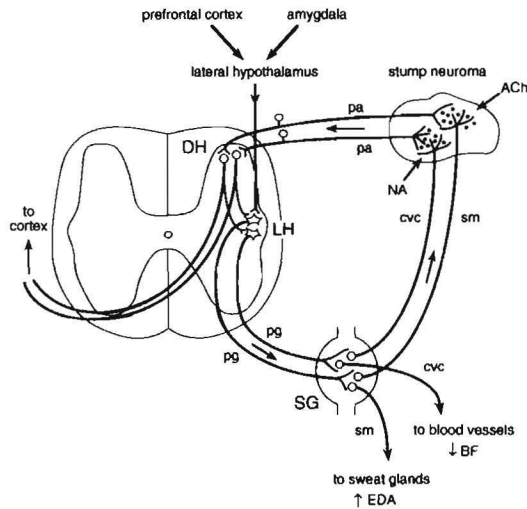


FIGURE 8. A mechanism of sympathetically generated phantom limb paresthesias. Spontaneous sympathetic activity or excitatory inputs descending from cortex (e.g., due to the perception of a salient event, loud noise, thought, feeling, etc.) increases the discharge rate of preganglionic (pg) sympathetic neurons with cell bodies in the lateral horn (LH) of the spinal cord and terminals in the sympathetic ganglion (SG). These neurons excite postganglionic noreadrenergic (NA) cutaneous vasoconstrictor (cvc) and cholinergic (ACh) sudomotor (sm) fibers that impinge on effector organs (vascular smooth muscle and sweat glands) in the stump and on sprouts from large diameter primary afferent (pa) fibers that have been trapped in a neuroma. The release of ACh and NA on effector organs results in increased electrodermal activity (EDA) and decreased blood flow (BF) to the stump. Release of these chemicals in the neuroma activates primary afferents that project to spinal cord dorsal horn (DH) cells subserving the amputated parts of the limb. These neurons, in turn, feed back to the preganglionic sympathetic neurons and project rostrally where the impulses contribute to the perceptions of phantom limb paresthesias. If DH cells have been sensitized due to injury, or nociceptive primary afferents are activated, the perceptions may be one of dysesthesias. (From Fields HL: Pain. New York, McGraw-Hill, 1987; with permission.)

acetylcholine,²⁹ and they discharge rapidly when these substances are present. In contrast, intact peripheral fibers do not show this chemosensitivity and thus have a higher threshold compared with regenerating sprouts. Second, the loss of afferent nerve impulses (deafferentation) resulting from amputation produces a disinhibition of cells in the dorsal horn and more rostral sensory structures, giving rise to the perception of a phantom limb.^{63,94} This consequence of deafferentation implies that the threshold for detecting sympathetically triggered afferent impulses arising from stump neuromas should be lower than at other, intact body sites since stump impulses would be subject to less inhibition upon reaching the spinal cord. This is consistent with the observation that the threshold for detecting sensations in the phantom limb during stimulation of the stump is lower than at the site of stimulation itself.¹²

Another possibility⁹ is that amputation leads to increased expression of alpha-adrenergic receptors located on mechanoreceptors or nociceptors in stump neuromas. This hypothesis would explain the perception of phantom limb paresthesias or dysesthesias in the absence of regional sympathetic hyperactivity or trophic changes

at the stump. Taken together, these observations may explain the puzzling finding that only after amputation does the (phantom) limb become the site of affectively- or cognitively-triggered sensations.

TREATMENT AND TREATMENT IMPLICATIONS

Most studies of PLP lack the rigorous control conditions and adequate sample sizes to conclude with certainty that specific treatments are more effective than no treatment or placebo treatment. Chabal's¹³ findings provide the strongest evidence in support of an adrenergic sympathetic-sensory coupling mechanism underlying stump pain and possibly PLP. The results of early studies showing that local anesthetic infiltration into the sympathetic chain^{58,59} and sympathectomy^{4,46} at least temporarily relieve PLP also suggest that sympathetic ganglion blocks or surgical sympathectomies are effective because they block the release of norepinephrine from the peripheral sympathetic terminals.

However, pain relief in response to a local anesthetic sympathetic block may be due to factors other than sympathetic blockade. Diffusion of the agent to the dorsal roots resulting in small fiber block or a systemic action of the local anesthetic are limitations of diagnostic sympathetic blocks that reduce the specificity of the test.⁷⁵ The lack of permanency of sympathectomy for PLP⁴⁶ may be due to a variety of factors, including inadequacy of diagnosis, extent of sympathectomy, surgical skill, and confusion about anatomy.¹¹ The finding that beta-adrenergic receptor blockade does not seem to be effective in relieving PLP⁸⁰ is consistent with the negative results of propranolol for treatment of SMP in nonamputees.¹⁰

Phantom limb pain and stump pain respond well to epidural or spinal administration of local anesthetics or opioids.³⁶⁻³⁸ While the relevant assessments to determine the presence of SMP were not established in these studies, the possibility remains that the continuous sympathetic blockade achieved by epidural infusions of local anesthetic agents may prove effective in the management of patients with SMP.¹¹ To date, neither the phentolamine test⁷⁶ nor regional infusions of guanethidine have been tried for PLP. Raja has published guidelines for evaluating patients suspected of having SMP.⁷⁵

Finally, mental stress and anxiety not only provoke transient increases in the intensity of phantom limb sensation and pain,^{3,82,87} but they also induce reflex bursting activity in cutaneous sudomotor and vasomotor sympathetic fibers.^{21,33} Moreover, distraction or attention diversion (and intense concentration) that reduces PLP^{65,73} also diminishes peripheral SNS activity.³³ These findings provide indirect support for the model shown in Figure 8 and suggest that relaxation training and other cognitive strategies directed at anxiety reduction and increasing self control may be effective in reducing PLP in certain amputees.

CONCLUSION

Despite frequent claims that the SNS is involved in phantom limb pain, surprisingly little direct evidence exists. With the exception of recent work by Chabal, studies have been correlational, showing associations between phantom pain or phantom paresthesias and peripheral sympathetic activity (e.g., surface skin temperature and skin conductance). These indirect data need to be supplemented by further microneurographic studies of sympathetic-sensory coupling in amputee neuromas as well as placebo-controlled diagnostic tests using guanethidine or phentolamine to ascertain the contribution of the SNS to painful and nonpainful phantom limbs.

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